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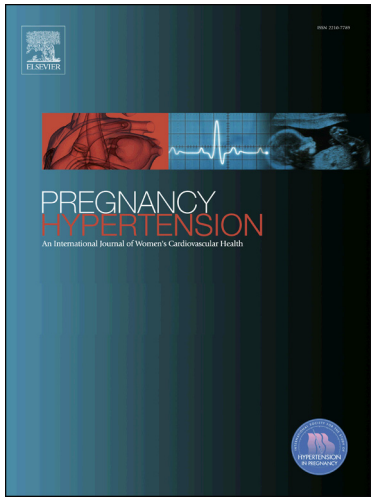

Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review

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PREDICTION OF ADVERSE MATERNAL OUTCOMES FROM PRE-ECLAMPSIA AND OTHER HYPERTENSIVE DISORDERS OF PREGNANCY: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity. The ability to predict these complications using simple tests could aid in management and improve outcomes. We aimed to systematically review studies that reported on potential predictors of adverse maternal outcomes among women with a hypertensive disorder of pregnancy.

Methods: We searched MEDLINE, Embase and CINAHL (inception - December 2016) for studies of predictors of severe maternal complications among women with a hypertensive disorder of pregnancy. Studies were selected in a two-stage process by two independent reviewers, excluding those reporting only on adverse fetal outcomes. We extracted data on study and test(s) characteristics and outcomes. Accuracy of prediction was assessed using sensitivity, specificity, likelihood ratios and area under the receiver operating curve (AUROC). Strong evidence of prediction was taken to be a positive likelihood ratio >10 or a negative likelihood ratio <0.1, and for multivariable models, an AUROC ≥0.70. Bivariate random effects models were used to summarise performance when possible.

Results: Of 32 studies included, 28 presented only model development and four examined external validation. Tests included symptoms and signs, laboratory tests and biomarkers. No single test was a strong independent predictor of outcome. The most promising prediction was with multivariable models, especially when oxygen saturation, or chest pain/dyspnea were included.

Conclusion: Future studies should investigate combinations of tests in multivariable models (rather than single predictors) to improve identification of women at high risk of adverse outcomes in the setting of the hypertensive disorders of pregnancy.

Keywords: Hypertensive disorders of pregnancy, pre-eclampsia, prognosis, prediction, maternal complications, review

INTRODUCTION

The hypertensive disorders of pregnancy (HDPs) complicate about 3-10% of pregnancies.[1-3]1-3 They are one of the major contributors to maternal and fetal mortality and morbidity globally, with approximately 30,000 maternal and 500,000 perinatal deaths attributed to the HDPs annually.[2,4] Maternal complications include eclampsia, stroke, and damage to the hepatic and renal organs.[2,5] Predicting the onset of these complications could aid in timely interventions such as increased surveillance, treatment of symptoms, transfer to higher care facility and delivery when necessary, which could reduce morbidity and mortality from the HDPs.[6,7]

Maternal risk factors used as criteria for severity classification by some international clinical practice guidelines do not accurately identify women at high risk of developing maternal complications.[8-11] While many studies have reported associations between certain biomarkers and adverse outcomes,[12-15] only a few studies have examined the accuracy of these tests in predicting adverse maternal outcomes; in other words, the accuracy of discriminating women who do experience serious morbidities versus those who do not at the individual level. The tests reported in these studies range from single markers to multiple markers combined in prediction models. Prediction models are increasingly used in clinical practice since they have the advantage of combining various factors to potentially provide more accurate predictions.[16] Regardless of the prediction method used, there is a need for the results from these studies be summarised and compared to determine if they give meaningful and accurate information to assist clinicians in the management of the HDPs.

Several systematic reviews have assessed the predictive ability of individual variables such as uric acid, maternal symptoms, and liver function tests for maternal and fetal complications

resulting specifically from pre-eclampsia.[17-20] To our knowledge, there have been no reviews assessing predictors for maternal complications resulting from all types of HDPs. This broader disease definition is important, as other HDPs still contribute substantially to the burden of the disease.[2,10,21] In addition, these reviews were conducted between 2006 and 2011 and since then the definition for HDPs, particularly pre-eclampsia, has evolved.[3] Furthermore, the studies included in these reviews solely assessed potential univariable predictors, thus the need to also review potential predictors combined in multivariable models. Therefore, we aimed to systematically review studies reporting the predictive ability, for both single and combined markers, of adverse maternal outcomes in women with HDPs.

METHODS

Protocol and registration

A protocol for this review has been registered on PROSPERO (registration number: CRD42017054328).

Eligibility criteria

The population of interest was women with a HDP: pre-eclampsia, gestational hypertension, or chronic (pre-existing) hypertension, as defined by the study (with study definitions documented). The predictors of interest were any tests measured to predict adverse maternal outcomes from HDP. The adverse maternal outcomes considered were severe complications from the HDPs which had been agreed upon in a Delphi Consensus in the PIERS (Pre-eclampsia Integrated Estimates of RiSks study) (https://pre-empt.cfri.ca/monitoring/fullpiers);[7] in addition, postpartum haemorrhage (PPH) and disseminated intravascular coagulation (DIC) were considered as these outcomes have been subsequently reported to be strongly linked with

HDPs.[21] Detailed inclusion and exclusion criteria and full list of outcomes of interest are shown in **Appendix S1**.

Search and selection Strategy

We searched MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), and EBM Reviews (Ovid) Library databases from their inception to December 2016. We also searched Google Scholar and grey literature sources (such as University of British Columbia cIRcle, government websites, etc.) for other potential articles. Web of Science was used for citation tracking of review and eligible articles and the reference lists of studies selected for inclusion were scanned to capture any articles that were not identified through the electronic search. The search terms included both subject headings terms and key words related to the HDPs, with methodological filters to identify prognostic test studies for maternal complications (**Appendix S2**).

All retrieved articles were screened independently for eligibility by two reviewers (UVU and DAD), first by title and abstract and then, by reviewing the full articles. Final selections were compared and any conflicts resolved by discussion and/or by a third reviewer (BP).

The predictive measures used were sensitivity, specificity, likelihood ratios (LRs), and area under the receiver operating characteristic curve (AUROC). Studies that reported none of these predictive measures were included only if adequate data were provided to calculate these measures. We excluded studies reporting both maternal and fetal outcomes as a combined outcome except in cases where the test prediction performance for the maternal outcomes could be separated. We also excluded studies that included any of the HDPs as one of the outcomes.

Data extraction and assessment of study quality

For each eligible study, information on population characteristics, tests used as predictors, measures and accuracy of prediction were extracted by one reviewer (UVU) and reviewed by another (DAD). Methodological quality assessment of the included studies was carried out using the QUIPS (Quality in Prognostic Studies) tools,[22] which have been validated and also used in similar studies.[23] The relevant study aspects that were scrutinized included methods of sampling and recruitment, adequate description of tests and outcomes, complete follow-up or handling of missing data explained, and sample size. In total, there were eight questions considered and one point was awarded for each assessment question that was met. In addition, studies reporting multivariable prediction models were assessed for internal and external validation. We considered studies with a total score of ≥ 7 as having a low risk of bias, 4-6 as medium risk of bias, and <4 as high risk of bias.

Data synthesis

We constructed 2×2 tables for each included study cross-classifying test results and the occurrence of adverse maternal outcomes. Measures of predictive performance were sensitivity, specificity, LRs, predictive values, and AUROC. These measures were either retrieved directly from the studies or calculated from constructed from raw data and 2×2 tables. LRs were used to provide interpretations for clinical usefulness as a measure that is independent of disease prevalence; for positive LRs (LR+), an LR of 5-10 and >10 were interpreted as having moderate and strong evidence to 'rule in' the disease respectively while for negative LRs (LR-), an LR of 0.1-0.2 and <0.1 were interpreted as having moderate and strong evidence to 'rule out' the disease respectively.[24] An AUROC ≥0.70 was also considered to reflect good discriminatory

ability for multivariable models.[25] Wherever possible, meta-analyses were conducted for similar tests predicting similar outcomes and having 3 or more 2×2 tables. Meta-analyses were performed using a bivariate meta-regression model, which uses a random effects approach, to calculate pooled estimates of the likelihood ratios.[26-28]

All statistical analyses were performed using R version 3.1.3 (The R Project for Statistical Computing).

RESULTS

Literature Search and identification results

Figure 1 summarizes article identification and selection. Of 2137 articles retrieved, we included 32 primary articles. Important exclusions presented an outcome that either included but were not restricted to women with a HDP (N=6), presented combined maternal and fetal outcomes (N=12), or studies for which a 2*2 table could not be constructed in order to calculate the diagnostic tests characteristics of interest (N=3) (see **Appendix S3** for excluded references).

Characteristics of included studies

Characteristics of the included studies are presented in Appendix S4. In brief, included articles were published between 1988 and 2017. Eleven were multicentre and 21 from single centres. Most studies (30/32) were cohort in design, usually prospective (24/30); one was a randomized trial and another was a case-control study. The countries where data were collected included Australia (N=8), the United Kingdom (N=8), Canada (N=7), New Zealand (N=7), USA (N=7), South Africa (N=5), India (N=3), The Netherlands (N=2), Pakistan (N=2), and one each of Iran, Spain, Tunisia, Turkey, Uganda, Mexico and Brazil.

In total, the number of independent women in the included studies was 9,360, with a mean or median gestational age at admission or recruitment ranging from 23 weeks to 36 weeks. The mean maternal age ranged from 23 to 35 years old, and 13% to 89% were nulliparous.

All included studies were published in English except for one study that was in French. Four studies presented external validation of a study.

Definition of HDPs

Four studies included women diagnosed with chronic hypertension; four studies also included gestational hypertension while the remaining studies reported solely on women with pre-eclampsia (including HELLP syndrome) or/and superimposed pre-eclampsia. Chronic hypertension was defined as high blood pressure (≥140/90 mmHg) before pregnancy or at <20 weeks gestation, and gestational hypertension as high blood pressure at ≥20 weeks gestation across all the studies; however, the definition of pre-eclampsia varied by the reference guideline used: the International Society for the Study of Hypertension in Pregnancy (ISSHP) (N=9),[29] American Congress of Obstetricians and Gynecologists (ACOG) (N=8),[30] National Institute for Health and Clinical Excellence (NICE) (N=1),[9] Society of Obstetricians and Gynaecologists of Canada (SOGC) (N=13),[3] or National High Blood Pressure Education Program (NHBPEP) (N=1)[31] guidelines.. Some studies also specifically mentioned the severity of the HDP such as severe pre-eclampsia,[32-38] early-onset pre-eclampsia,[33,38] or mild chronic hypertension[33] (Appendix Table S4).

Quality of studies

The quality of the included studies is summarised in Figure 2 and Appendix S5. The studies scored well with respect to adequacy of population selection description, appropriateness of the

patient spectrum/representativeness, and adequacy of test and outcome descriptions. However, of the 32 studies, only 14 mentioned complete follow up or explained withdrawals, 11 reported on handling of missing data, six reported sample size calculations, and two of five multivariable model studies reported both internal and external validation; all four external validation studies were classified as having a medium to high risk of bias. As a result, only eight studies were ranked as being at low risk of bias, 22 at medium risk, and two at high risk.

Predictors, outcomes and data synthesis

The predictors reported in the studies included demographics and pregnancy characteristics (e.g., gestational age), maternal signs and symptoms of pre-eclampsia [including oxygen saturation (SpO_2)], urinary protein excretion, laboratory abnormalities associated with pre-eclampsia, and/or biomarkers (**Table 1**).

The prevalence of adverse maternal outcomes ranged from 1.1% to 34.2%. Nine studies reported on single outcomes, most commonly eclampsia (N=6), and placental abruption (N=6). Most studies (23/32) reported on composite outcomes; these usually included the common single outcomes as well as thrombocytopenia, PPH, ascites and hepatic rupture.

The 32 studies resulted in 74 2×2 tables. **Table 1** presents the sensitivities, specificities, likelihood ratios, and AUROCs for the predictor variables. We were unable to perform meta-analysis on the majority of predictors evaluated. The only predictor meeting our *a priori* criteria for meta-analysis, specifically having 3 published reports of effect using a similar outcome type, was the sFlt1/PlGF ratio for the prediction of composite maternal outcomes.

Univariable predictors

Signs and symptoms

In the univariable analyses, the maternal symptoms[39-42] evaluated were: headache (N=3 studies), visual disturbance (N=3), nausea or vomiting (N=2), right upper quadrant pain or epigastric pain (N=2), chest pain or dyspnoea (N=2), abdominal pain and vaginal bleeding (N=1), and hyperreflexia (defined as "vivid" deep tendon reflexes) or "non-specific viral symptoms" (not defined) (N=1 study each). The signs evaluated were oxygen saturation (N=1), and BP [N=3].[40,43-44].

Only non-specific viral symptoms had moderate LR+ for ruling in composite adverse maternal outcomes[39] while headache, visual symptoms and hyperreflexia each had moderate LRs (-) for ruling out eclampsia (LRs between 0.1 and 0.2).[40] Non-specific viral symptoms and oxygen saturation of <93% also had reported AUROCs of ≥0.7 suggesting good discriminatory ability for the prediction of composite adverse maternal outcomes. The usefulness of each of these symptoms was demonstrated in only one study.

Blood pressure

One of the signs evaluated was blood pressure, which was assessed in three studies[40,43-44] as systolic (N=2), diastolic (N=1), or mean arterial pressure (MAP, N=1). The outcomes being predicted in these studies were eclampsia and placental abruption, for women with either pre-eclampsia or mild chronic hypertension. The cut-off for SBP evaluated were >140 and ≥ 160 mmHg[40,43] while the cut-off for DBP was > 90 mmHg;[43] MAP was assessed at > 105 mmHg.[44] Although significant associations (p-values <0.05) between blood pressure and adverse outcomes

were presented in these studies, none of them showed a clinically useful measure for blood pressure as a prognostic test for adverse maternal outcomes.

Proteinuria

Proteinuria was assessed in six studies,[40,45-49] using measurements of 24h urinary protein excretion (N=5), spot protein/creatinine ratio (N=1), spot albumin/creatinine ratio (N=1) and/or urinary dipstick testing (N=3).

Only the study by Bouzari *et al*[45] reported a moderate LR- for ruling out placental abruption using 24-hour urine proteinuria, at a cut-off of 1750mg [LR- of 0.1 (95% CI: 0.0–0.6)] with an AUROC of 0.78. No other study reported a clinically useful measure for ruling in or out adverse maternal outcomes using proteinuria testing.

Laboratory tests

The laboratory tests assessed were: platelet count (N=4 studies),[39,44,50-51] serum creatinine (N=1),[40] serum uric acid (N=3),[40,53-54] international normalized ratio (INR, N=1),[52] aspartate transaminase (AST, N=4),[39-40,52,55] alanine transaminase (ALT, N=2),[39,52] lactate dehydrogenase (LDH, N=2),[39,52] serum albumin[52] and total bilirubin[52] (N=1 each).

None of the laboratory tests had a useful LR+ to rule in adverse maternal outcomes. Only serum uric acid had a moderate LR- for ruling out eclampsia in one study (LR- of 0.1 (95% CIs: 0–0.9).[54] However, AST, ALT, and LDH were reported to have good discriminatory abilities, with AUROCs of >0.70 for prediction of adverse maternal outcome in the study by Kozic *et al*[52]

Biomarkers

Placental growth factor (PlGF) only (N=1 study),[56] soluble fms-like tyrosine kinase-1 (sFlt1) to PlGF ratio (N=4),[57-60] and Neutrophil Gelatinase-Associated Lipocalin (NGAL, N=1)[61] were evaluated as predictors. The study on PlGF alone was reporting on the prediction of PPH while the studies on sFlt1:PlGF ratio and NGAL were evaluating the prediction of composite adverse maternal outcomes. None of these biomarkers were reported to have clinically useful measures to either rule in or rule out adverse maternal outcomes. The meta-analysis for the sFlt1: PlGF ratio for predicting composite outcomes demonstrated poor pooled LRs:- LR+ 1.7 (95% CIs: 1.2–2.0)] and LR- of 0.6 (95% CIs: 0.5–0.8) (tau^2 for heterogeneity=0).

Multivariable predictors

Six studies evaluated a combination of multiple variables to predict a composite of adverse maternal outcomes.[42,62-65] Four of these multivariable studies were part of the PIERS studies: the fullPIERS model,[7] miniPIERS model,[62] extended miniPIERS model with SpO_2,[63] and a combined cardiorespiratory symptom model by Millman *et al*[42] for the prediction of the PIERS composite outcome; the outcomes in the two other studies by Chan *et al*[64] and Girling *et al*[65] also included some components of the PIERS outcomes such as renal failure, thrombocytopenia, liver disease and pulmonary oedema. The miniPIERS model,[62] and extended miniPIERS model with SpO_2,[63] were the only multivariable models that included women with all HDPs, while the others were for women with (super-imposed) pre-eclampsia. The most commonly used predictors in these models were chest pain and dyspnoea (N=4 models), oxygen saturation and gestational age (N=3), and AST (N=2). Three of the multivariable models (fullPIERS model,[7] miniPIERS model,[62] and extended miniPIERS model with SpO_2[63]) reported moderate to high LR+ for ruling in adverse maternal outcomes (LR+ of 5 and above) and four of them (models by Millman, fullPIERS model,[7] miniPIERS model,[62] extended miniPIERS model with SpO_2) reported

AUROCs of ≥0.7; all of these were predicting PIERS adverse outcomes. The model with the highest AUROC was reported in the study by von Dadelszen *et al*[7] (AUROC 0·88 (95% CI 0·84–0·92) and also had the highest LR+ of 26.5 to strongly rule in composite adverse maternal outcomes. The multivariable model, called the fullPIERS model, included six variables: gestational age of disease onset, platelet count, serum creatinine, AST, chest pain or dyspnea and SpO_2. For details of the model variable coefficients, please see **Appendix S6**.

External validation

Four studies on external validation were included.[66-69] All assessed the fullPIERS model by von Dadelszen *et al*.[7] AUROCs were >0.7 (N=2 studies)[67-68] and 0.68 (95% CI 0·60–0·76) in the study by Hadley; AUROC was not reported in the study by Agrawal *et al*. Likelihood ratios were reported in only two studies and these studies reported moderate LRs (+) for ruling in adverse outcomes.[66-67] Although all four studies were assessing the validity of the fullPIERS model, there were substantial differences between the fullPIERS and external validation populations, such as disease spectrum, setting, and management (**Table S4b**). Due to these case-mix differences, we refrained from pooling the results of these studies.

DISCUSSION

Main findings

Our systematic review included 32 studies of women with HDPs that explored the ability of various tests to predict adverse maternal outcomes. There was substantial heterogeneity in the characteristics of the populations included in these studies and the outcomes used. This heterogeneity likely contributed to the inconsistent results found for the predictive performance of the evaluated tests. Overall, the univariable predictors that had moderate performance as a rule

in test were "non-specific viral symptoms" and 24hr urinary protein, and as rule-out tests were headache, visual symptoms, hyperreflexia, and serum uric acid. Non-specific viral symptoms, oxygen saturation <93%, AST, ALT, and LDH were the only univariable tests that had good discrimination with a reported AUROC of ≥ 0.7. However, these tests were either assessed in only one study (e.g. hyperreflexia and "non-specific viral symptoms") or were evaluated in multiple studies but performed poorly in them. As such, individual tests were interpreted as lacking strong evidence of clinical usefulness. In addition, the definition of non-specific viral symptoms was not clearly stated in the study.[39]

In our review, oxygen saturation showed the most promise as a prognostic test for the hypertensive mother in univariable and especially in multivariable models. Other tests to consider when combining variables in multivariable models include headache, visual symptoms, AST, chest pain or dyspnea and gestational age, based on their inclusion in well performing multivariable models, which had also been internally validated. However, the performance of the multivariable models may have been due to the presence of other possible good predictors in the models driving the effect (**Appendix S6**), thus, some of these tests (e.g. AST) may require further investigations as possible predictors for adverse maternal outcomes of HDPs.[72]

The best performing multivariable model included gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, creatinine and AST as predictors of composite maternal outcomes in women with pre-eclampsia and superimposed pre-eclampsia.[7] This model was externally assessed in four studies that were included in this review. Although three of these validation studies showed a good discriminatory performance (AUROC >0.7), two of these studies were underpowered. In addition, there were case-mix differences between the studies and the development study which could have affected the model performance.

Comparison with literature and guidelines

Except for one study on predicting eclampsia, our findings are similar to the study by Thangaratinam *et al*[17] which reported that proteinuria was a poor predictor of maternal complications in pre-eclampsia based on the pooled positive and negative LRs in their study. Another review by Moris *et al*[20] concluded that there was insufficient evidence to recommend proteinuria as a prognostic test for the prognosis of adverse maternal outcomes in pre-eclampsia. Proteinuria is also not recommended as a test for the prediction of adverse maternal outcomes for women with HDPs by ACOG, AOM, and SOGC guidelines; however, the NICE guideline calls for large high quality prospective studies to determine the best methods of measurement and threshold for predicting adverse outcomes.[9]

In a systematic review of maternal symptoms as predictors of adverse outcomes,[19] epigastric pain and visual disturbance were reported to be the most useful predictors based on their AUROCs; however, this was not the case in our review for epigastric pain. Also, contrary to the findings in the review by Koopmans *et al*[70] and Thangaratinam *et al*,[71] uric acid did not show any clinical usefulness in the prediction of maternal outcomes in our review except for eclampsia. Noteworthy is the difference between the inclusion criteria and outcomes of interest between these reviews and ours. In the reviews, HELLP syndrome was considered as an adverse outcome and was one of their most common outcomes; however, for our review, HELLP syndrome was one of our inclusion criteria for HDP because it has been recognised as part of the spectrum of pre-eclampsia rather than an outcome.[30] Therefore, it is possible that the performances of epigastric pain and uric acid in these reviews were related to women with HELLP rather than predictive of adverse maternal outcomes that measure end-organ failure.

A review by Thangaratinam *et al*[8] reported that liver enzyme tests (AST, ALT and LDH) were moderate predictors of combined maternal and fetal complications in women with pre-eclampsia. Although, AST, ALT and LDH did not have any strong clinical utility in univariable analyses based on LRs, their AUROCs in the individual studies suggested good discrimination and may therefore be considered for further investigation. This is also in line with the NICE guideline which recommends that more studies for kidney and liver function, and coagulation for the prediction of adverse outcomes are needed.[9]

Strengths and limitations

Our review is the first to review potential predictors of maternal complications among women with all types of HDPs. Including all HDPs improve the clinical applicability because it includes a broader population of women at risk and not all women initially present with pre-eclampsia at admission. We were able to systematically identify and collate the performance of possible predictors using updated definitions for HDPs and with no restrictions on language or year of publication. We ran our search terms again in July 2017 to ensure that we covered any recent eligible publications. Our review also included the use of multivariable models which have not been assessed in any previous review.

The majority of the included studies in this review were deemed to be of low or moderate quality. Many of the studies were underpowered and some of the multivariable models were not externally validated; thus the results from these studies may not be applicable in a different setting or population. However, we did not exclude these studies because we were interested in reviewing any tests with potential maternal prognostic value for HDPs and also due to sparse literature in the study area. The only articles not included were ones that did not meet the

inclusion criteria for severe maternal outcomes; for example, we excluded a new prognostic study by Allotey *et al*[73] which included preterm delivery are one of their composite maternal outcomes as we did thought that this qualified more as a perinatal than a maternal outcome. The methodological issues in the included studies and the heterogeneity in population characteristics affect our ability to draw any strong conclusions in our review. The limited numbers of studies evaluating similar tests and outcomes also made it impossible to synthesize most of the predictors using meta-analyses.

CONCLUSION

Prediction of adverse maternal outcomes from the HDPs is key to optimal management, including timing of delivery and planning the most appropriate place of care.[4,15] Overall, the multivariable models performed better than the univariable tests. However, sufficiently-powered external validation studies using a similar population as the development studies are still required for most of these models. Our review highlights the need for better quality studies in prediction and supports the use of a combination of predictors for better chances of prediction of adverse maternal outcomes.

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DISCLOSURES

None.

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Table 1. Accuracy of tests in the prediction of adverse maternal outcomes in women with HDP, *N* = 32 studies

UNIVARIABLE TESTS, N=24 studies								
Author, Year	**Test / cut-off**	**Outcome**	**Total (outcome rate %)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**	**AUROC (95% CI)**
Signs and/or symptoms								
Aziz et al. 2011	Headache	Composite	74 (27%)	30.0 (11.9-54.3)	46.3 (32.6-60.4)	0.6 (0.3-1.1)	1.5 (1.0-2.3)	0.40 (0.20-0.50)
Ben Salem et al. 2003	Headache	Eclampsia	120 (34.2%)	97.6 (85.6-99.9)	26.6 (17.6-37.9)	1.3 (1.2-1.5)	0.1 (0-0.7)	-
Yen et al. 2011	Headache	PIERS Composite	2020 (7.1%)	-	-	-	-	0.535 (0.47-0.58)
Aziz et al. 2011	Vomiting	Composite	74 (27%)	10.0 (1.2-31.7)	77.9 (64.4-88.0)	0.5 (0.1-1.8)	1.2 (0.9-1.4)	0.40 (0.30-0.50)
Yen et al. 2011	Nausea/vomiting	PIERS Composite	2020 (7.1%)	-	-	-	-	0.54 (0.48-0.60)
Ben Salem et al. 2003	Visual symptoms	Eclampsia	120 (34.2%)	85.4 (70.1-93.9)	65.8 (54.2-75.9)	2.5 (1.8-3.5)	0.2 (0.1-0.5)	-
Yen et al. 2011	Visual symptoms	PIERS Composite	2020 (7.1%)	-	-	-	-	0.50 (0.45-0.56)
Yen et al. 2011	Abdominal pain or vaginal bleeding	PIERS Composite	2020 (7.1%)	-	-	-	-	0.57 (0.47-0.67)
Aziz et al. 2011	Epigastric pain	Composite	74 (27%)	10.0 (1.2-31.7)	70.4 (56.4-82.0)	0.3 (0.1-1.3)	1.3 (1.0-1.6)	0.4 (0.3-0.5)
Yen et al. 2011	RUQ or epigastric pain	PIERS Composite	2020 (7.1%)	-	-	-	-	0.605 (0.545-0.664)
Millman et al. 2011	Chest pain and/or dyspnoea	PIERS Composite	1534 (6.1%)	-	-	-	-	0.59 (0.52-0.65)
Millman et al. 2011	Chest pain and/or dyspnoea	Non-respiratory PIERS Composite	1534 (4.4%)	-	-	-	-	0.53 (0.45-0.60)

Yen et al. 2011	Chest pain or dyspnoea	PIERS Composite	2020 (7.1%)	-	-	-	-	0.58 (0.52-0.64)
Millman et al. 2011	SpO_2 <93%	PIERS Composite	1534 (6.1%)	-	-	-	-	0.71 (0.65-0.77)
Millman et al. 2011	SpO_2 <93%	Non-respiratory PIERS Composite	1534 (4.4%)					0.64 (0.57-0.71)
Aziz et al. 2011	Non-specific viral symptoms	Composite	74 (27%)	65.0 (40.8-84.6)	87.0 (75.1-94.6)	5.0 (2.3-10.7)	0.4 (0.2-0.7)	0.80 (0.60-0.90)
Ben Salem et al. 2003	Vivid deep tendon reflexes	Eclampsia	120 (34.2%)	97.6 (85.6-99.9)	46.8 (35.6-58.3)	1.8 (1.5-2.3)	0.1 (0.0-0.4)	-
Blood pressure (BP)								
Ben Salem et al. 2003	sBP ≥ 160 mmHg	Eclampsia	120 (34.2%)	92.7 (79.0-98.1)	24.1 (15.4-35.2)	1.2 (1.0-1.4)	0.3 (0.1-1.0)	-
Ankumah et al. 2014	sBP and/or dBP >140/90 mmHg	Placental abruption	759 (1.4%)	36.4 (12.4-68.4)	62.8 (59.2-66.3)	1.0 (0.4–2.1)	1.0 (0.6–1.9)	-
Witlin et al. 1999	MAP >105 mmHg	Eclampsia	445 (9.0%)	92.5 (78.5-98.0)	3.2 (1.8-5.6)	1.0 (0.9–1.0)	2.3 (0.9–8.0)	-
Witlin et al. 1999	MAP >105 mmHg	Placental abruption	445 (7.2%)	87.5 (70.1-95.9)	2.2 (1.1-4.2)	0.9 (0.8–1.0)	5.7 (1.9–17.8)	-
Proteinuria								
Ben Salem et al. 2003	Dipstick >3+	Eclampsia	120 (34.2%)	85.3 (70.1-93.9)	53.2 (41.7-64.4)	1.8 (1.4-2.4)	0.3 (0.1-0.6)	-
Ben Salem et al. 2003	24h urine >3g/d	Eclampsia	120 (34.2%)	36.6 (22.6-53.1)	91.1 (82.0-96.1)	4.1 (1.8-9.3)	0.7 (0.6-0.9)	-
Bouzari et al. 2014	24h urine >1.75g/d	Placental abruption	289 (5.9%)	94.1 (69.2-99.7)	63.7 (57.5-69.3)	2.6 (2.1–3.1)	0.1 (0.0–0.6)	0.777
Gangaram et al. 2009†	Spot urine ACR ≥300mg/g	Composite	155 (2.6%)	0	55.0 (46.7-63.0)	-	1.8 (1.8-1.8)	
Hall et al. 2002	24h urine increased by ≥2g	Placental abruption	74 (13.5%)	30.0 (8.1-64.6)	59.4 (46.4-71.2)	0.7 (0.3-2.0)	1.2 (0.8-1.8)	-
Hall et al. 2002	24h urine increased by ≥2g	Ascites	74 (10.8%)	62.5 (25.9-89.8)	63.6 50.8-74.9)	1.7 (0.9-3.2)	0.6 (0.2-1.5)	-
Hall et al. 2002	24h urine increased by ≥2g	Pulmonary edema†	74 (1.4%)	0 (0-94.5%)	60.3 (48.1-71.3)	-	1.7 (1.6-1.7)	

Hall et al. 2002	24h urine increased by ≥2g	Eclampsia†	74 (1.4%)	100 (5.5-100)	61.6 (49.5-72.6)	2.6 (1.9-3.5)	-	-
Payne et al. 2011	Dipstick	PIERS Composite	2002 (5.3%)	-	-	-	-	0.55 (0.49-0.61)
Payne et al. 2011	Spot urine PRCR	PIERS Composite	2002 (5.3%)	-	-	-	-	0.48 (0.42-0.55)
Payne et al. 2011	24hr urine	PIERS Composite	2002 (5.3%)	-	-	-	-	0.55 (0.47-0.63)
Schiff et al. 1996	24h urine increased by ≥2g	Placental abruption	2002 (5.3%)	40 (7.3-83.0)	63.9 (50.6-75.5)	1.1 (0.4-3.4)	0.9 (0.5-2.0)	-
Laboratory tests								
Aziz et al. 2011 2011	Platelets $\leq 100 \times 10^5$/L	Composite	74 (27%)	70.0 (45.7-88.1)	20.4 (10.6-33.5)	0.9 (0.6-1.2)	1.5 (0.6-3.4)	0.40 (0.30-0.60)
Laskin et al. 2011	Platelets $\leq 100 \times 10^9$/L	PIERS Composite	1405 (10.8%)	15.8 (10.6-22.8)	92.2 (90.5-93.6)	2.0 (1.3–3.1)	0.9 (0.9–1.0)	-
Witlin et al. 1999	Platelets <60,000/mm^3	Placental abruption	445 (7.2%)	37.5 (21.7-56.3)	85.0 (81.1-88.2)	2.5 (1.5–4.1)	0.7 (0.6–1.0)	-
Yucesoy et al. 2005	Platelets <50,000/mm^3	Eclampsia	44 (29.5%)	38.5 (15.1-67.7)	64.5 (45.4-80.2)	1.1 (0.5–2.5)	1.0 (0.6–1.5)	-
Yucesoy et al. 2005	Platelets <50,000/mm^3	Placenta abruption	44 (11.4%)	40.0 (7.3-83.0)	64.1 (47.1-78.3)	1.1 (0.4–3.5)	0.9 (0.4–2.0)	-
Yucesoy et al. 2005	Platelets <50,000/mm^3	Disseminated intravascular coagulation	44 (18.2%)	75.0 (35.6-95.5)	72.2 (54.6-85.2)	2.7 (1.4–5.2)	0.3 (0.1–1.2)	-
Yucesoy et al. 2005	Platelets <50,000/mm^3	Acute renal failure	44 (15.9%)	71.4 (30.3-94.9)	70.3 (52.8-83.6)	2.4 (1.2–4.8)	0.4 (0.1–1.3)	-
Yucesoy et al. 2005	Platelets <50,000/mm^3	Maternal mortality	44 (9.1%)	25.0 (1.3-78.1)	62.5 (1.3-76.8)	0.7 (0.1–3.8)	1.2 (0.6–2.2)	-
Kozic et al. 2011	INR	PIERS Composite	2008 (5.1%)	-	-	-	-	0.65 (0.58-0.71)
Ben Salem et al. 2003	Creatinine >100µmol/L	Eclampsia	120 (34.2%)	39.0 (24.6-55.5)	81.0 (70.3-88.6)	2.1 (1.1-3.7)	0.8 (0.6-1.0)	-
Ben Salem et al. 2003	Uric acid ≥350 µmol/L	Eclampsia	120 (34.2%)	82.9 (67.4-92.3)	65.8 (54.2-92.3)	2.4 (1.7-3.4)	0.3 (0.1-0.5)	-
Livingston et al. 2014	Uric acid >345 µmol/L	PIERS Composite	1487 (13.3%)	80.2 (70.8- 87.6)	28.2 (25.9-30.7)	1.1 (1.0–1.2)	0.7 (0.5–1.0)	0.62 (0.56-0.69)

Yassaee et al. 2003†	Uric acid ≥6mg/dL	Maternal mortality†	103 (8.7%)	100 (62.9-100)	53.2 (42.6-63.4)	2.1 (1.7–2.7)	0	-
Yassaee et al. 2003†	Uric acid ≥6mg/dL	Eclampsia	103 (12.6%)	92.3 (62.1-99.6)	54.4 (43.6-64.9)	2.0 (1.5–2.7)	0.1 (0–0.9)	-
Aziz et al. 2011	ALT ≥70 IU/L	Composite	74 (27%)	55.0 (31.5-76.9)	25.9 (15.0-39.7)	0.7 (0.5-1.1)	1.7 (0.9-3.4)	0.4 (0.3-0.5)
Kozic et al. 2011	ALT	PIERS Composite	2008 (5.1%)	-	-	-	-	0 .73 (0 .67-0.79)
Aziz et al. 2011	AST ≥70 IU/L	Composite	74 (27%)	60.0 (36.1-80.9)	42.6 (29.2-56.8)	1.1 (0.7-1.6)	0.9 (0.5-1.8)	0.50 (0.40-0.60)
Ben Salem et al. 2003	AST >30 IU/L	Eclampsia	120 (34.2%)	63.4 (46.9-77.4)	70.9 (59.4-80.3)	2.2 (1.4-3.3)	0.5 (0.4-0.8)	-
Kozic et al. 2011	AST	PIERS Composite	2008 (5.1%)	-	-	-	-	0.73 (0.67-0.79)
Romero et al. 1988	AST 2SD above mean	Pulmonary edema	275 (1.1%)	66.7 (12.5-98.2)	79.4 (74.0-84.0)	3.2 (1.4–7.5)	0.4 (0.1–2.1)	-
Romero et al. 1988	AST 2SD above mean	Eclampsia	275 (2.5%)	71.4 (30.3-94.9)	80.2 (74.8-84.7)	3.6 (2.1–6.1)	0.4 (0.1–1.2)	-
Aziz et al. 2011	LDH ≥600 IU/L	Composite	74 (27%)	75.0 (50.9-91.3)	55.6 (41.4-61.9)	1.7 (1.1-2.5)	0.5 (0.2-1.0)	0.7 (0.6-0.8)
Kozic et al. 2011	LDH	PIERS Composite	2008 (5.1%)	-	-	-	-	0.74 (0.68-0.81)
Kozic et al. 2011	Serum albumin	PIERS Composite	2008 (5.1%)	-	-	-	-	0.63 (0.57-0.69)
Kozic et al. 2011	Total bilirubin	PIERS Composite	2008 (5.1%)	-	-	-	-	0.68 (0 61-0.74)
Biomarkers								
Ghosh et al. 2012	Serum PlGF <122pg/mL	Postpartum hemorrhage (PPH)	766 (8.7%)	73.1 (60.7-82.9)	76.7 (73.3-79.7)	3.14 (2.57-3.82)	0.35 (0.24-0.52)	-
Leaños-Miranda et al. 2013	Serum sFlt-1/PlGF ratio ≥871	Composite	501 (9.6%)	52.1 (37.4-66.5)	77.9 (73.8-81.6)	2.36 (1.71-3.26)	0.61 (0.46-0.83)	-
Palomaki et al. 2015	Serum Flt-1/PlGF ratio >85	Composite	237 (8.9%)	61.9 (38.7–81.0)	69.4 (62.8–75.4)	2.0 (1.4–3.0)	0.5 (0.3–1.0)	-
Rana et al. 2013†	Serum Flt-1/PlGF	Composite	97 (8.2%)	100	51.7	2.1	∞	-

	ratio≥85			(59.7–100)	(40.9–62.3)	(1.7–2.6)		
Saleh et al. 2016†	Serum Flt-1/PlGF ratio≥85	Composite	62 (9.7%)	100 (51.7–100)	10.7 (4.4–22.6)	1.1 (1.0–1.2)	-	-
Scazzochio et al. 2013	Maternal NGAL >100ng/mL	Composite	67 (17.9%)	41.7 (16.5-71.4)	65.5 (51.3-77.4)	1.2 (0.6-2.6)	0.9 (0.5-1.5)	-
MULTIVARIABLE TESTS, N=6 studies								
Chan et al.† 2005	Spot urine PRCR >500 and maternal age >35 years	Composite	321 (34%)	10.2 (5.4–17.9)	100 (97.8–100)	-	0.9 (0.8–1.0)	0.67 (0.55-0.71)
Girling et al. 1997†	AST 30 U/L ALT 32 U/L Bilirubin 14 U/L GGT 41 U/L	Composite	35 (20%)	100 (56.1-100)	57.1 (37.4-75.0)	2.3 (1.5–3.6)	-	-
Millman et al. 2011	Chest pain and/or dyspnoea and SpO_2	PIERS Composite	1534 (6.1%)	-	-	-	-	0.73 (0.67-0.78)
Payne et al. 2014	miniPIERS model ǂ 25% predicted probability	PIERS Composite	2081 (12.5%)	41.4 (35.4–47.6)	91.9 (90.5–93.1)	5.1 (4.1–6.3)	0.6 (0.6–0.7)	0.79 (0.74–0.80)
Payne et al. 2015	miniPIERS model ǂ and SpO_2, 25% predicted probability	PIERS Composite	852 (17.3%)	49.6 (40.3–58.8)	91.5 (89.2–93.4)	5.9 (4.3–7.9)	0.6 (0.5–0.7)	0.81 (0.76-0.86)
von Dadelszen et al. 2011	GA, chest pain or dyspnea, SpO_2, platelet count, creatinine and AST; 30% predicted probability	PIERS Composite	2023 (5%)	44.9 (34.5–55.3)	98.4 (97.6-98.9)	26.5 (17.4–40.2)	0.6 (0.5–0.7)	0.88 (0.84–0.92)
EXTERNAL VALIDATION STUDIES, N=4 studies								
Agrawal et al. 2015	30% predicted probability	PIERS composite	322 (18.3%)	25.0 (15.1–38.1)	95.4 (91.9–97.5)	17.5 (8.52-36.1)	0.8 (0.7–0.9)	-
Akkermans et al. 2014	30% predicted probability	PIERS composite	216 (14.8%)	81.3 (63.0–92.1)	98.4 (94.9–99.6)	49.8 (16.0–155.0)	0.2 (0.1–0.4)	0.97 (0.94–0.99)
Hadley et al. 2016*	-	PIERS composite	503 (12.3%)	-	-	-	-	0.68 (0.60-0.76

Ukah et al. 2015	30% predicted probability	PIERS composite	757 (14.0%)	45.0 (0.36–0.55)	92.4 (84.9–99.9)	5.9 (4.2–8.4)	0.2 (0.1–0.5)	0.77 (0.72–0.82)

† contains some zero cells; * Abstract only ; ǂ miniPIERS includes parity, gestational age, chest pain/dyspnea, headache or visual symptoms, vaginal bleeding with abdominal pain; sBP, and dipstick proteinuria

ACR (albumin:creatinine ratio); AUROC (Area under the receiver operating characteristic curve); dBP (diastolic blood pressure); GA (gestational age); INR (international normalized ratio); LR+ (Positive likelihood ratio); LR- (Negative likelihood ratio); MAP (mean arterial pressure); NGAL (neutrophil gelatinase-associated lipocalin); *PIERS (pre-eclampsia integrated estimate of risk); PRCR (protein:creatinine ratio); RUQ (Right upper quadrant pain); sBP (systolic blood pressure); SD (standard deviation); SpO_2 (oxygen saturation)*

ONLINE SUPPLEMENTS

S1. Inclusion and exclusion criteria

Selection criteria	**Inclusion**	**Exclusion**
Population	Studies recruiting patients with any hypertensive disorder of pregnancy (HDPs) – gestational hypertension, chronic hypertension, pre-eclampsia, super-imposed pre-eclampsia and HELLP syndrome	Studies not recruiting women with HDP
Intervention/ Study design	Studies reporting risk prediction or prognosis tests for adverse maternal outcomes resulting from HDPs or studies that provide data that can be used to calculate these tests. Prognostic tests include at least one of the following: area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, likelihood ratios, negative or positive predictive value.	Studies that do not report prognosis tests OR studies not presenting sufficient data for calculation
Comparators	None	
Outcomes	Primary outcome measures were studies including any PIERS adverse maternal outcomes (https://pre-empt.cfri.ca/monitoring/fullpiers)	Studies without outcome measures OR Studies that report on combined fetal and maternal outcome and the

	or/and Postpartum haemorrhage (PPH); disseminated intravascular coagulation (DIC)	prediction of maternal outcome cannot be separated.
Language	None	
Publication year limit	None	

S2. Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
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1 exp Hypertension, Pregnancy-Induced/ (31573)

2 (HDP or HDPs).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (940)

3 (preeclamp* or pre-eclamp*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (35884)

4 ((Chronic hypertens* or essential hypertens* or preexisting hypertens* or pre-existing hypertens*) adj3 (pregnan* or gestation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (653)

5 HELLP Syndrome/ (1609)

6 HELLP.mp. (2473)

7 or/1-6 (41093)

8 nomograms/ (1952)

9 Models, statistical/ (78055)

10 logistic models/ (108873)

11 "Predictive Value of Tests"/ (168044)

12 Risk assessment/ (207143)

13 clinical risk assessment*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (302)

14 prognos* model*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2879)

15 predict* model*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20780)

16 (AUC or AUROC or area under the receiver or ROC or ROCs or Receiver operating curve*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (96577)

17 sensitivit*.mp. (935762)

18 specificit*.mp. (926124)

19 (LR* or likelihood ratio*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (45658)

20 negative predictive value*.mp. (34619)

21 positive predictive value*.mp. (35114)

22 or/8-21 (1990826)

23 ((risk* or predict* or prognos*) adj6 (adverse or complication* or outcome* or event* or situation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (286836)

24 ((risk* or predict* or prognos*) adj6 (morbid* or mortality)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (104862)

25 ((risk* or predict* or prognos*) adj6 (Hepatic or GCS or Glasgow or Stroke or Cortical or RIND or retinal or Dialysis or renal or PIS or Positive inotropic support or Infusion or Myocardial or MI or Intubation or thrombocytop?nia)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (128207)

26 23 or 24 or 25 (466662)

27 7 and 22 and 26 (828)

Appendix S3. Rejected Articles

Combined HDP and outcome (N= 6)

1. ElizaldeValdes V.M., TellezBecerril G.E., LopezAceves LJ. Construction and validation of a risk factor scale for complications of pre-eclampsia. Clinica e Investigacion en Ginecologia y Obstetricia 2016 01 Jul 2016;43(3):110-121

2. Orabona R., Gerosa V., Gregorini M.E., Pagani G., Prefumo F., Valcamonico A., et al. The prognostic role of various indices and ratios of Doppler velocimetry in patients with pre-eclampsia. Clin.Exp.Hypertens. 2015 01 Feb 2015;37(1):57-62

3. Tokmak A, Güney G, Aksoy RT, Guzel AI, Topcu HO, Keçecioglu TS, et al. May maternal anti-mullerian hormone levels predict adverse maternal and perinatal outcomes in preeclampsia? J MATERN FETAL NEONAT MED 2015 08;28(12):1451-1456

4. Sak M.E., Evsen M.S., Soydinc H.E., Turgut A., Ozler A., Sak S., et al. Risk factors for maternal mortality in eclampsia: analysis of 167 eclamptic cases. Eur.Rev.Med.Pharmacol.Sci. 2012 Oct 2012;16(10):1399-1403

5. Lumbanraja SN. Determining the maternal characteristics that predicts the adverse outcomes for patients with preeclampsia. Journal of Health and Translational Medicine 2013 2013;16(1):1-6

6. tive value of urinary albumin: Creatinine ratio in pregnancy. Archives of Disease in Childhood: Fetal and Neonatal Edition 2014. June 2014;99:A137

*2*2 table not possible (N= 3)*

Dave A., Maru L., Jain A. LDH (Lactate Dehydrogenase): A Biochemical Marker for the Prediction of Adverse Outcomes in Pre-eclampsia and Eclampsia. Journal of Obstetrics and Gynecology of India 2016 01 Feb 2016;66(1):23-29

Oztas E., Ozler S., Ersoy A.O., Iskender C.T., Sucak A., Ergin M., et al. Increased levels of serum clusterin is associated with intrauterine growth restriction and adverse pregnancy outcomes in preeclampsia. J.Perinat.Med. 2016 01 Apr 2016;44(3):269-275

Tumanyan S.S., Tumanyan S.V., Rymashevski AN. Predictors of renal dysfunction and its correction in women with preeclampsia and alimentary obesity. Anesteziol.Reanimatol. 2015 01 Jan 2015;60(1):42-44

Combined maternal and fetal outcomes (N=12)

1. Allotey J, Marlin N, Mol BW, et al. Development and validation of prediction models for risk of adverse outcomes in women with early-onset pre-eclampsia: Protocol of the prospective cohort PREP study. *Diagnostic and Prognostic Research*. 2017;1(1). doi: 10.1186/s41512-016-0004-8. Parrish M., Griffin M., 2. Morris R., Darby M., Owens M.Y., Martin Jr. JN. Hyperuricemia facilitates the prediction of maternal and perinatal adverse outcome in patients with severe/superimposed preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2010 December 2010;23(12):1451-1455

3. Robb A., Elia E., Hemming K., Price M., Riley R., FrenchConstant A., et al. Could urinary albumin: Creatinine ratio be used to predict adverse outcomes in suspected preeclampsia?. BJOG: An International Journal of Obstetrics and Gynaecology 2016. April 2016;123:17

4. van der Tuuk K, Koopmans CM, Groen H, Aarnoudse JG, van den Berg PP, van Beek JJ, et al. Prediction of progression to a high risk situation in women with gestational hypertension or mild pre-eclampsia at term. Aust.N.Z.J.Obstet.Gynaecol. 2011 Aug;51(4):339-346

5. De Oliveira L., Peracoli J.C., Peracoli M.T., Korkes H., Zampieri G., Moron A.F., et al. SFlt-1/PlGF ratio as a prognostic marker of adverse outcomes in women with early-onset preeclampsia. Pregnancy Hypertension 2013 July 2013;3(3):191-195

6. Lumbanraja SN. Determining the maternal characteristics that predicts the adverse outcomes for patients with preeclampsia. Journal of Health and Translational Medicine 2013 2013;16(1):1-6

7. Moore A.G., Young H., Keller J.M., Ojo L.R., Yan J., Simas T.A.M., et al. Angiogenic biomarkers for prediction of maternal and neonatal complications in suspected preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2012 December 2012;25(12):2651-2657

8. Nadeau H.C., Tita A.T.N., Anderson S., Tang Y., Dimperio L., Harper LM. Predicting adverse pregnancy outcomes associated with chronic hypertension: A classification and regression tree (CART) Analysis. American Journal of Obstetrics and Gynecology.Conference: January 2016;214(1 SUPPL. 1):S245

9. Rana S., Hacker M., Merport A., Salahuddin S., Verlohren S., Perschel F., et al. Angiogenic factors and risk of preeclampsia related adverse outcomes in twin pregnancies. Pregnancy Hypertension 2012. July 2012;2(3):273-274

10. Robb A., Elia E., Hemming K., Price M., Riley R., FrenchConstant A., et al. Could urinary albumin: Creatinine ratio be used to predict adverse outcomes in suspected preeclampsia?. BJOG: An International Journal of Obstetrics and Gynaecology 2016. April 2016;123:17

11. Sibiude J., Guibourdenche J., Dionne M.D., Le Ray C., Anselem O., Serreau R., et al. Placental Growth Factor for the Prediction of Adverse Outcomes in Patients with Suspected Preeclampsia or Intrauterine Growth Restriction. PLoS ONE 2012;7(11) (pagination):Arte Number: e50208. ate of Pubaton: 28 No 2012

12. Chaiworapongsa T, Romero R, Korzeniewski SJ, Cortez JM, Pappas A, Tarca AL, et al. Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: A prospective study. Journal of maternal-fetal

S4. Characteristics of included studies, *N* = 32 studies

INDEPENDENT STUDIES, N=28 studies								
Author, Year	**Study design**	**Country(ies)**	**Time period**	**Type of HDP**	**Maternal characteristics**	**Outcome(s)**	**Prediction method**	**Tests**
Ankumah et al. 2014	Multicentre RCT	USA	May 1991-Jun 1995	Mild chronic hypertension	Mean age: 30 Mean GA: 19.8 Nulliparous: 18.2%	Placental abruption	Univariable	Blood pressure
Aziz et al. 2011	Retrospective review	India	Jan 2005-Dec 2009	HELLP syndrome	Mean age: 26.6 Mean GA: 32.9 Nulliparity: 62.2%	Composite: DIC, ARF, PPH, Placental abruption, cerebral or pulmonary edema, liver infarcts or rupture, or a subcapsular liver hematoma or maternal death	Univariable	Epigastric pain; vomiting; headache; visual symptoms; non-specific viral symptoms; platelets; AST; ALT; LDH
Ben Salem et al. 2003	Case-control	Tunisia	Jan 1995-Jun 2000	Pre-eclampsia	Mean age: 30 NulliParity: 38.3%	Eclampsia	Univariable	sBP; dBP; headache; visual symptoms; hyperreflexia; proteinuria; uric acid; serum creatinine; AST
Bouzari et al. 2014	Retrospective cohort	Iran	2000-2010	Pre-eclampsia	Mean age: 29.5	Placental abruption	Univariable	24h proteinuria
Chan et al. 2005	Retrospective cohort	Australia	1998-2001	Pre-eclampsia	Mean Age: 30 Nulliparity: 73%	Composite: renal insufficiency (creatinine >90 umol/L), liver disease (AST >40 U/L), cerebral irritation (hyperreflexia with clonus or repeated visual scotomata, requiring magnesium sulphate) and thrombocytopenia (platelets <150* 10^9/L)	Multivariable logistic regression	Spot urine PRCR and maternal age at diagnosis
Gangaram et	Prospective	South Africa	January	Gestational	Median GA: 33	Composite: Placental	Univariable	Spot urine ACR

al. 2009	cohort		2006	hypertension and pre-eclampsia	Nulliparity: 12.9%	abruption, eclampsia		
Ghosh et al. 2012	Prospective cohort	India	Mar 2009-Jun 2011	Early onset preeclampsia <34 weeks	GA presentation: 23 Median Age: 23 Nulliparity: 76%	Postpartum hemorrhage (PPH) defined as a blood loss of >1500 ml and/or the need for a blood transfusion, for a caesarian delivery and >1000 ml and/or the need for a blood transfusion, in case of a vaginal birth	Univariable	Serum PlGF
Girling et al. 1997	Prospective cross-sectional	UK	-	Pre-eclampsia	GA presentation: - Mean age: 29	Composite: acute renal failure requiring dialysis, profound oliguria needing central venous pressure monitoring and renal support, and spontaneous pulmonary oedema	Multivariable	Abnormal liver function tests (AST, ALT, bilirubin, GGT)
Hall et al. 2002	Prospective cohort	South Africa	Apr 1992 – Mar 1997	Early onset, severe pre-eclampsia	Mean Age: 27 Mean GA: 29.5	Placental abruption, ascites, pulmonary edema, eclampsia	Univariable	24h proteinuria
Kozic et al. 2011	Multicentre prospective review	Canada, Australia, New Zealand, UK	Sep 2003 – Jan 2010	Pre-eclampsia	Mean: 31 Nulliparity: 71.1%	PIERS Composite	Univariable	AST, ALT, LDH, albumin, total bilirubin, INR
Laskin et al. 2011	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sep 2003 – Jan 2010	Pre-eclampsia	Median age: 31 Median GA: 33.7 Nulliparity: 72.6%	PIERS composite outcome	Univariable	Platelet count
Leaños-Miranda et al. 2013	Prospective cohort	Mexico	-	Pre-eclampsia	GA presentation: 32 Mean Age: 28.3 Nulliparous: 43.5%	Composite: maternal mortality and any of the following serious maternal morbidities: hepatic	Univariable	Serum sFlt-1/PlGF ratio

						hematoma or rupture (confirmed by ultrasound or laparotomy), pulmonary edema (clinical diagnosis and with radiographic confirmation), need for positive inotropic support, intubation (other than solely for caesarean section), acute renal failure (creatinine ≥198 µmol/L), and placental abruption (clinical or pathological).		
Livingston et al. 2014	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sept 2003 – Dec 2011	Pre-eclampsia	Median Age: 31 Median GA: 35 Nulliparity: 73.8%	PIERS composite outcome	Univariable	Uric acid
Millman et al. 2011	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sept 2003 – Jan 2010	Pre-eclampsia	Median Age: 31 Median GA:34.1 Nulliparity: 89.2%	PIERS composite outcome	Univariable and multivariable	SpO_2; chest pain and/or dyspnea
Palomaki et al. 2015	Prospective cohort	USA	Jul 2009 – Jun 2012	HDP	Mean GA: 30	Composite (Placental abruption, Acute renal failure, DIC, Pulmonary edema)	Univariable	sFlt-1/PlGF ratio
Payne et al. 2011	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sept 2003 – Jan 2010	Pre-eclampsia	Median age: 31 Median GA: 36 Nulliparity: 71.4%	PIERS composite outcome	Univariable	Proteinuria (dipstick, spot PRCR, 24h protein)
Payne et al. 2014	Multicentre prospective cohort	Uganda, South Africa, Brazil, Pakistan	Jul 2008 – Mar 2012	Any HDP	Median age: 28 Median GA: 35.3 Nulliparity: 46.1%	PIERS composite outcome	Multivariable logistic regression	Parity, GA at assessment, chest pain/dyspnea, headache/visual disturbances, vaginal bleeding with abdominal pain, sBP, dipstick proteinuria

Payne et al. 2015	Multicentre prospective cohort	South Africa, Pakistan	Jan 2011 – Dec 2013	All HDP	Mean age: 28 Nulliparity: 47.7%	PIERS composite outcome	Multivariable logistic regression	Parity, GA at assessment, Chest pain/dyspnea, Headache/visual disturbances, Vaginal bleeding with abdominal pain, sBP, dipstick proteinuria and SpO_2
Rana et al. 2013	Prospective cohort	USA	Jul 2009 – Oct 2010	Pre-eclampsia	Mean Age: 32 Mean GA: 35 Nulliparity: 70.1%	Composite: abnormal liver function test and platelets, placental abruption, pulmonary edema, cerebral hemorrhage, seizure (in the absence of an underlying seizure disorder), acute renal failure (creatinine41.5mg/dL) or maternal death	Spearman rank correlation	sFlt1/PlGF ratio
Romero et al. 1988	Retrospective review	USA	Jan 1981 – Sep 1984	GH, Pre-eclampsia and superimposed pre-eclampsia	Mean age: 25.5 Nulliparity: 71.6%	Pulmonary edema, eclampsia	Univariable	AST
Saleh et al. 2016	Prospective	Netherlands	Sep 2011 – Aug 2013	Pre-eclampsia	Mean age: 32 Mean GA: 30	Composite: Pulmonary edema, Acute renal failure	Binary logistic analysis	sFlt1/PlGF ratio
Scazzochio et al. 2013	Prospective	Spain	Sep 2010 – Sep 2012	Severe preeclampsia <34 weeks	Mean age: 32 Mean GA: 30.3 Primiparity: 58.2%	Composite: Acute renal failure and pulmonary edema	Univariable	Maternal Neutrophil Gelatinase-Associated Lipocalin (NGAL)
Schiff et al. 1996	Retrospective review	USA	Jan 1990 – Dec 1994	Severe pre-eclampsia	Mean Age: 23 Mean GA: 31.2 Nulliparity: 50%	Placental abruption	Univariable	24h urine proteinuria
von Dadelszen et al. 2011	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sep 2003 – Jan 2010	Pre-eclampsia	Median age: 31 Median GA: 35 Nulliparity: 71.3%	PIERS composite outcome	Multivariable logistic regression	GA, Chest pain or dyspnoea, oxygen

								saturation, platelet count, creatinine, and AST
Witlin et al. 1999	Prospective	USA	Mar 1992 – Jan 1997	Severe pre-eclampsia	Mean Age: 22.8	Eclampsia, placental abruption	Univariable	Mean arterial pressure (MAP), Platelet count
Yassaee et al. 2003	Cohort	Iran	1986-2001	Severe pre-eclampsia	-	Maternal mortality, eclampsia	Univariable	Uric acid
Yen et al. 2011	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sep 2003 – Jul 2009	Pre-eclampsia	Mean Age: 32 Mean GA: 34.4 Nulliparity: 71.3%	PIERS composite outcome	Univariable	Nausea and vomiting; Headache; Visual disturbances; Right upper quadrant or epigastric pain; Abdominal pain or vaginal bleeding; Chest pain or dyspnea
Yucesoy et al. 2005	Prospective cohort	Turkey	-	HELLP syndrome	Mean age: 26.5 Mean GA: 31.5 Nulliparity: 29.5%	Eclampsia, placenta abruption, DIC, acute renal failure, maternal mortality	Univariable	Platelet count
EXTERNAL VALIDATION STUDIES, N=4 studies								
Author, Year	**Study design**	**Country(ies)**	**Time period**	**Type of HDP**	**Maternal characteristics**	**Outcome(s)**	**Primary study**	**Case-mix compared to primary study**
von Dadelszen et al. 2011	Multicentre prospective cohort	Canada, New Zealand, Australia, UK	Sep 2003 – Jan 2010	Pre-eclampsia	Median age: 31 Median GA: 35 Nulliparity: 71.3%	PIERS composite outcome	Primary model being externally validated	Only pre-eclampsia in high-income countries, all GAs, tertiary centres, expectant management
Agrawal et al. 2014	Prospective cohort	India	-	Pre-eclampsia	Mean GA: 24.8 Nulliparity: 48.6%	PIERS composite	von Dadelszen et al. 2011	Low- and middle-income countries (LMICs)
Akkermans et al. 2014	Multicentre prospective cohort	Netherlands	Apr 2000 – May 2003	Severe early-onset pre-eclampsia, eclampsia, HELLP syndrome or	Mean age: 29.5 Mean GA: 30.3 Nulliparity: 69.9%	PIERS composite	von Dadelszen et al. 2011	GA <34 weeks, high-risk cohort only

				hypertension-associated fetal growth restriction				
Hadley et al. 2016*	Retrospective cohort	USA	-	Pre-eclampsia	-	PIERS composite	von Dadelszen et al. 2011	Conservative management
Ukah et al. 2015	Prospective cohort	USA	Jul 2008 – Mar 2012	Any HDP	Median age: 28 Median GA: 35.3 Nulliparity: 46.1%	PIERS composite	von Dadelszen et al. 2011	Any HDPs, LMICs

* Abstract only with limited information

ACR (albumin:creatinine ratio); ALT (alanine transaminase); ARF (acute renal failure); AST (aspartate transaminase); dBP (diastolic blood pressure); DIC (disseminated intravascular coagulation); GA (gestational age); GGT (gamma-glutamyl transferase); HDPs (hypertensive disorders of pregnancy); INR (international normalized ratio); LDH (lactate dehydrogenase); LMICs (low- and middle-income countries); MAP (mean arterial pressure); NGAL (neutrophil gelatinase-associated lipocalin); *PIERS (pre-eclampsia integrated estimate of risk); PlGF (placental growth factor); PPH (postpartum haemorrhage); PRCR (protein:creatinine ratio); RCT (randomized controlled trial); RUQ (Right upper quadrant pain); sBP (systolic blood pressure); SD (standard deviation); sFlt-1 (soluble fms-like tyrosine kinase-1); SpO_2 (oxygen saturation)*

S5. Quality of included studies scores

Study	Population selection	Appropriate study design	Complete follow up/withdrawals explained	Appropriate patient spectrum	Test description	Handling of missing data	Outcome description	Sample size	Internal Validation	External validation	Score
Agrawal 2015	1	1	0	0	1	0	1	0	0	0	4
Akkermans 2014	1	1	1	0	1	1	1	0	0	0	6
Ankumah 2014	1	1	1	1	1	1	1	0	0	0	7
Aziz 2011	1	0	0	1	1	0	1	0	0	0	4
Ben Salem 2003	1	0	1	0	1	0	1	0	0	0	4
Bouzari 2014	1	0	1	1	1	1	1	0	0	0	6
Chan 2005	1	0	1	1	1	0	1	0	0	0	5
Gangaram 2009	1	1	1	1	1	0	1	0	0	0	6
Ghosh 2012	1	1	0	1	1	0	1	0	0	0	5
Girling 1997	1	1	0	1	1	0	1	0	0	0	5
Hadley 2016	1	1	0	1	0	0	1	0	0	0	4
Hall 2002	1	1	0	1	1	0	1	0	0	0	5
Kozic	1	1	1	1	1	0	1	0	0	0	6

2011											
Laskin 2011	1	1	0	1	1	0	1	0	0	0	5
Leaños-Miranda 2013	1	1	0	1	1	0	1	0	0	0	5
Livingston 2014	1	1	1	1	1	1	1	0	0	0	7
Millman 2011	1	1	0	1	1	0	1	0	0	0	5
Palomaki 2015	1	1	1	1	1	1	1	1	0	0	8
Payne 2015 (miniPIERS + SpO2)	1	1	0	1	1	1	1	1	1	0	8
Payne 2011 (proteinuria)	1	1	1	1	1	1	1	0	0	0	7
Payne 2014 (miniPIERS)	1	1	1	1	1	1	1	1	1	1	10
Rana 2013	0	1	0	0	1	0	1	0	0	0	3
Romero 1988	1	0	1	1	1	1	1	0	0	0	6
Saleh 2016	1	1	0	1	1	0	1	1	0	0	6
Scazzochio 2013	1	1	1	1	1	1	1	0	0	0	7
Schiff 1996	1	1	0	1	1	0	1	0	0	0	5

Ukah 2015	1	1	0	0	1	0	1	1	0	0	5
von Dadelszen 2011	1	1	1	1	1	1	1	1	1	1	10
Witlin 1999	1	1	0	1	1	0	1	0	0	0	5
Yassaee 2003	1	0	0	0	1	0	1	0	0	0	3
Yen 2011	1	1	0	1	1	0	1	0	0	0	5
Yucesoy 2005	1	1	0	1	1	0	1	0	0	0	5

Assessment Questions: 1 = Yes; 0 = No; **Score:** <4 = High risk of bias; 4-6 = Medium risk of bias; ≥7 = Low risk of bias

S6. Multivariable model variable coefficients

Study name	Model variables	Coefficients	AUROC
Chan 2005	Spot urine protein/creatinine	0.003	0.67
	Age	0.058	(0.55-0.71)
Girling 1997	ALT	Not stated	-
	AST		
	Bilirubin		
	GGT		
Millman	chest pain and/or dyspnea	1.404	0.73
2011	Oxygen saturation	–0.362	(0.67-0.78)
Payne 2014	multiparity	-0.298	0.79
(miniPIERS)	GA	-1.07	(0.74–0.80)
	Chest pain/dyspnea	0.847	
	Headache or visual symptoms	0.422	
	Vaginal bleeding with abdominal pain	1.18	
	sBP	1.34	
	dipstick proteinuria	-0.218	
Payne 2015	Oxygen saturation	–0.434	0.81
(miniPIERS + SpO_2)	+ miniPIERS variables	+ miniPIERS	(0.76-0.86)

von Dadelszen 2011	GA	-0.054	0·88
(fullPIERS)	Chest pain or dyspnoea,	1.23	(0·84–0·92)
	platelet count	0.207	
	creatinine	-0.027	
	AST	0.010	
	Oxygen saturation	0.03681	
	Creatinine *platelets	0.00025	
	Platelets*AST	-0.000069	
	Platelets* oxygen saturation	-0.0026	
	Platelets2	0.00004	
	AST2	-0.0000031	

S7. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 & S4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6 & S1

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 & Fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9 & S4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

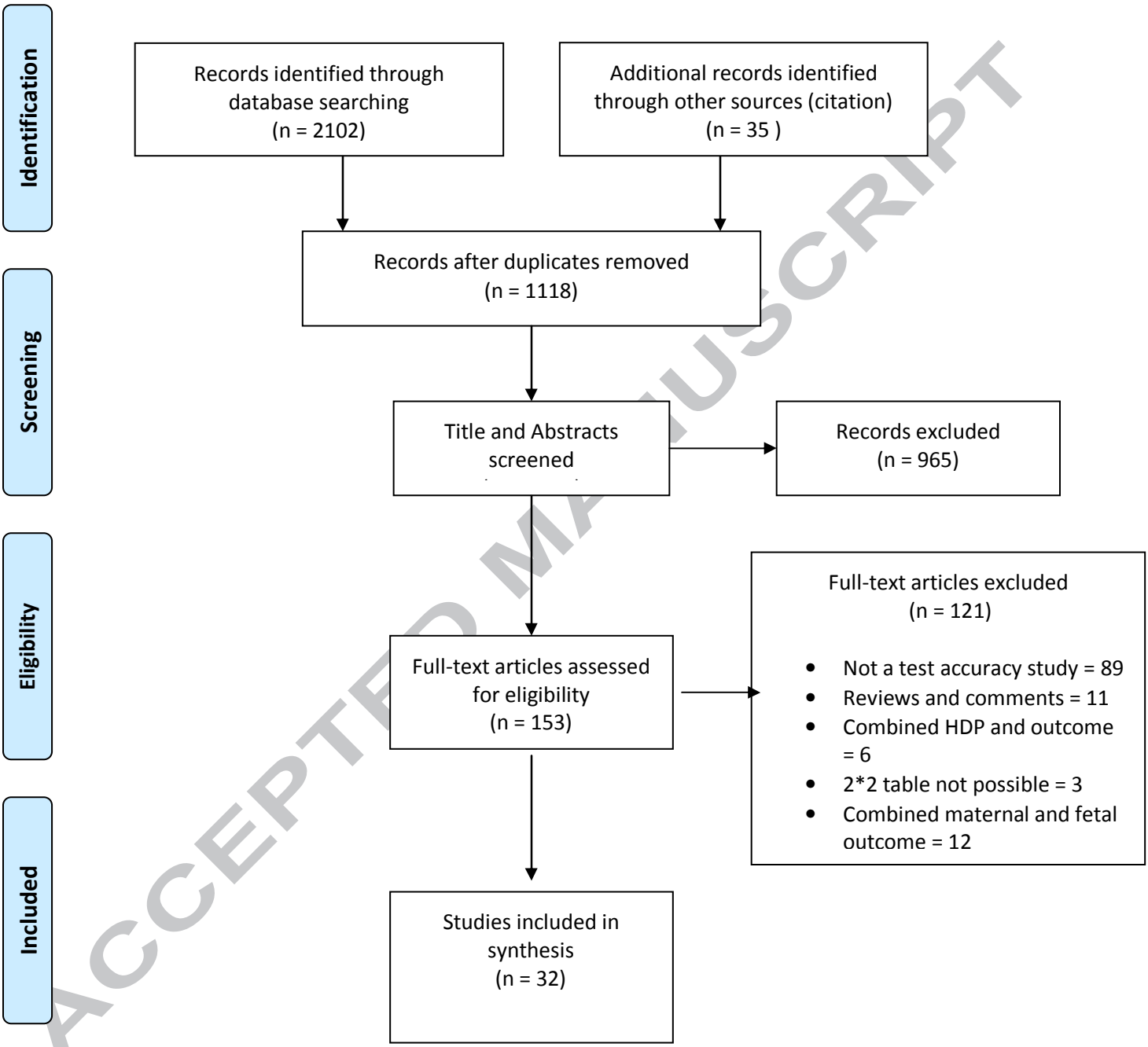

Figure 1. PRISMA flow diagram showing study selection process

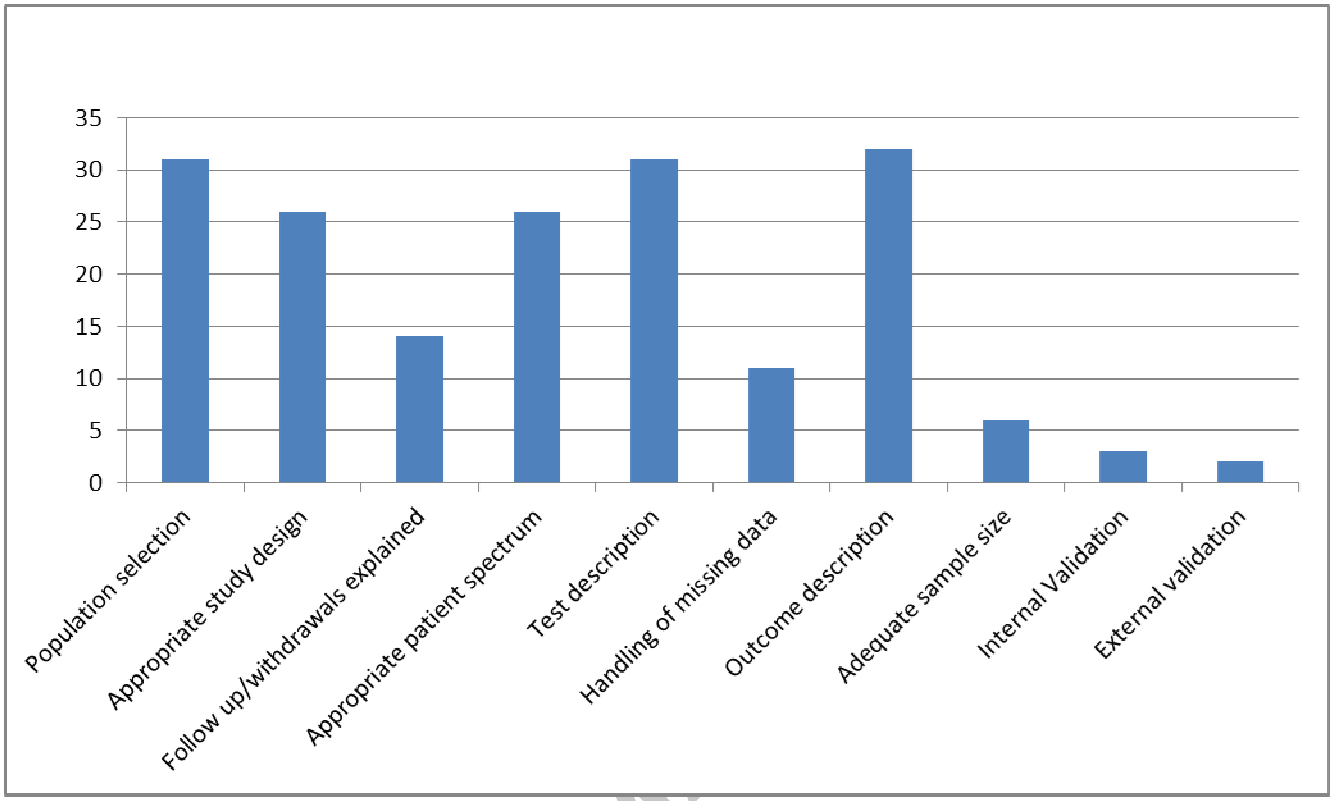

Figure 2. Quality assessment of the included studies

HIGHLIGHTS

- The ability to predict maternal outcomes from HDPs will guide management of such pregnancies
- We have systematically reviewed potential predictors of severe maternal complications among women with all types of HDPs including both univariable and multivariable tests
- Multivariable models perform better than do individual tests in predicting adverse maternal outcomes from the HDPs.
- Potential tests to consider in multivariable models are: gestational age, headache, visual symptoms, chest pain, dyspnea, oxygen saturation, and AST,
- There is need for better quality studies in prediction and combination of predictors for better chances of prediction of adverse maternal outcomes.